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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,074	10/01/2003	Mark Page	ICC-133.1 (4564/90735)	8455

24628 7590 03/16/2006

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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 03/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,074	PAGE ET AL.	
	Examiner	**Art Unit**	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,18,28,32-34 and 48-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,18,28,32-34 and 48-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 February 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date *4-18-05*.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Currently, claims 1, 18, 28, 32-34, and 48-51 are pending in the application.

2. In the prior action, the (second) Requirement for Restriction mailed on July 28, 2005, claims 1, 7-9, 18-20, 22-24, 26, 28, 32-34, 39, and 45-53 were pending and subject to the requirement.

3. In the December 27, 2005 Response, the Applicant made the appropriate elections (with traverse).

In addition, the Applicant amended claims 1, 18, 28, and 48; and cancelled claims 7-9, 19, 20, 22-24, 26, 39, 45-47, 52, and 53 from the application.

4. Applicant's election with traverse of Group II in the Response filed on December 27, 2005 is acknowledged. The traversal is on the ground(s) that the claims other than claim 1 fall within the scope of the elected invention. In view of the arguments and the amendments to the claims such that the pending claims fall within the scope of the elected invention, claims 18, 28, 32-34, and 48-51 are rejoined with claim 1.

The requirement is still deemed proper with respect to the other claims (now cancelled) of Groups I and III, and is therefore made FINAL.

Priority

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Under 35 U.S.C. § 120, an application

may claim priority to an earlier application "which is filed by an inventor or inventors named in the previously filed application." Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 in that the present application does not share any named inventor with applications 10/082,014 or 10/080,299, to which priority is claimed as a CIP.

Thus, although the claim to priority is acknowledged, because the Applicant has not met all of the conditions for claiming priority to the earlier applications, the present Applicant is not afforded benefit of a priority date prior to February 21, 2003- the filing date for application 10/372,076 which shares two inventors with the present application.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on April 18, 2005, is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

7. It is noted that, in the IDS listing, the reference WO 99/52549 was cited twice. One of the instances has been crossed out from the listing.

Drawings

8. The drawings are objected to because the images of Figures 8-10 are not clear enough to be deciphered. It is noted that, because the application incorporates by reference the teachings of application 10/082014, in which the drawings can be made out enough to be read, amendment of the present application to include more clear images of these Figures would not be considered new matter.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

9. The disclosure is objected to because of the following informalities: the phrase "that can be used to overcome over come the potential problems" in the third paragraph of page 14 contains a redundant term (the second form of overcome). It is suggested that the phrase "over come" be deleted.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 18, 28, 32-34, and 48-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is treated as representative. This claim reads on the use of a chimeric Hepatitis B core (HBc) chimeric protein. The HBc protein is described as comprising at least the sequence of "positions 4 through about 75" of a native HBc sequence, and, in one embodiment, as comprising one to three cysteine residues at amino acid positions corresponding to positions "–20 to about +1 from the N-terminus of SEQ ID NO: 1." It is unclear if this limitation requires that presence of amino acids in positions corresponding to at least positions 2 and 3 in this embodiment.

This is because the claims indicate that the sequence comprising these cysteines includes cysteines in any of positions –20 to +1 of the HBc sequence. In order to correspond to such positions, it would appear that additional residues must be inserted so as to result in the placement of a cysteine in +1 position, rather than in the +3 position. However, it is not clear if this was the intent of the Applicant, or if the Applicant intended that the cysteine residues may be directly peptide bonded to the required amino acid of position 4 of the HBc sequence.

With respect the claim 18, it is noted that claim 5, but not claim 4 is required by the claim. However, the claim is otherwise drawn to similar subject matter as the other independent claims.

Clarification is required.

12. Claims 1, 18, 28, 32-34, 48-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what is meant by the claimed step of "maintaining said patient." It appears from the claim language that this step is intended to indicate that the treatment is maintained until the T-cell immune response is induced. This is also the interpretation that will be applied for the purposes of this action. However, it is not clear if this is the case, or if the claim is merely requiring that the patient is maintained under supervision until such time that the T-cell response is activated and confirmed.

Clarification is required.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1, 18, 28, 32-34, 48-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to methods to induce an immune response against activated T-cells against Hepatitis B virus through the administration of a chimeric HBc protein. These chimeric HBc proteins are described as comprising insertions of chemically non-reactive

sequences into the immunodominant loop of the protein (between residues 75 and 85 of the HBc sequence). Independent claims 1 and 48 are drawn to genera of methods which comprise the administration of chimeric HBc proteins with up to 20% of the residues in the native HBc sequence having been conservatively substituted. Independent claim 18 is drawn to a genus of methods wherein the HBc sequences may have up to 10% of the sequence substituted. Thus, the claims are drawn to genera of methods comprising the administration of variant HBc proteins, comprising up to 10 or 20 percent difference from the native HBc sequence, wherein the proteins are capable of inducing a T-cell response against HBV.

In making a determination as to whether a claimed invention has been adequately described to show that the applicant the courts have identified certain elements that may be considered. Among those elements are the knowledge in the particular field, the extent and content of the prior art, the maturity of the technology, and predictability of the aspect at issue. See e.g., Capon v. Eshhar, 76 U.S.P.Q. 2d 1078, at 1085 (CAFC 2005). The courts have also provided more specific guidance as to means for providing support for generic claims, such as are in the present case. The following quotation from section 2163 of the Manual of Patent Examination Procedure provides a brief discussion of the support required for generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Such support may be found through disclosure of a representative number of species, absent other factors such as uncertainty in the operation of undisclosed species [see e.g., In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973)], or through disclosure of a functional characteristic of the claimed genus coupled with a known or disclosed non-functional characteristic (structure) that correlates to the function.

In the present application, no species of the claimed invention have been provided. However, although the application does not disclose a chimeric HBc comprising an inserted chemically non-reactive loop that induces an anti-HBc T-cell response, the application does disclose several naturally occurring HBc sequences. See e.g., Figure 1 (SEQ ID NOs: 1-6). In addition, it is noted that the art teaches that the HBc protein is capable of inducing anti-HBV T-cell responses. See e.g., Jung et al., J Virol 69: 3358-68 (stating on page 3358 that the core antigen is known to play a predominant role as an inducer of T helper function and a target for CTL responses). The application does not disclose substitution variants of the sequence that maintain the ability to induce an anti-HBV T-cell response.

In contrast to the teachings of the application, the art teaches that, although proteins tend to permit some level of amino acid substitution, the results of any specific such modification are generally unpredictable in the absence of specific guidance as to the relationship between a targeted residue and the function and structure of the protein. See e.g., Bowie et al., Science 247:1306-10. Other teachings in the art also note that a change in a single residue can change the antigenic profile of the protein. See e.g., Riffkin et al., Gene 167:279-83. The art also provides similar teachings with respect to modifications to T-cell epitopes within a protein. See e.g., Sarobe et al., J Clin Invest 102:1239-48. In particular, the Sarobe reference specifically teaches the modification of epitopes of the HCV virus, and demonstrates that different modifications to these epitopes have different effects. See e.g., page 1243 (teaching that different epitope modifications had different effects on the recognition of the epitopes by T-cells, and the ability of the epitopes to induce CTL activity). Thus, the art teaches that there is significant uncertainty in the effects of amino acid substitutions both generally, and with respect to substitutions in an epitope, and therefore in the operability of polypeptides comprising such substitutions.

The Sarobe reference also notes that, in order for the modified epitope to be useful, it must not only be able to induce an immune response, but that response must also be directed against the target antigen. See e.g., page 1246, right column (first full paragraph). In view of the teachings of Riffkin (that a single substitution can change the antigen profile of a protein), and the stated concern is Sarobe, there is also uncertainty in the art regarding a modified protein to be capable of inducing an immune response against its naturally occurring form.

In the present case, the rejected claims permit the substitution of one in every 5 or 10 amino acid residues. Similarly, the art teaches that T-cell epitopes generally comprise between 8 and 10 residues in length (e.g., Sarobe, page 1239, right column). Thus, even if it is assumed that there is an epitope in each 8-10 residues of the HBc polypeptide of the present claims (which does note appear to be the case- see e.g., the teachings of Jung above), the claims permit at least one modification in each of the these epitopes. As was indicated by the above teachings in the art, those in the art would have had little certainty in the effects that any of these potential modifications would have on the ability of the resultant HBc particles to either induce a T-cell response at all, or to induce such a response directed against the Hepatitis B virus.

Thus, the art provides several grounds of uncertainty regarding the operability of modified HBc proteins encompassed by the claims to induce the desired anti-HBV T-cell responses. In addition, the application provides little, if any, guidance as to what modifications can be made to the HBc proteins so as to retain the ability to induce such responses. For these reasons, and as the application provides no operable species of the claim genera, much less a representative number, there is insufficient descriptive support in the application to demonstrate possession of the claimed genera of methods, involving the use of any HBc with up to 10 or 20 % substituted residues to induce an anti-HBV immune response.

15. Claims 1, 18, 28, and 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inducing or enhancing an anti-HBV T-cell immune response, does not reasonably provide enablement for methods of treating chronic hepatitis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. More specifically, the claims are rejected because the Applicant has not established that the claimed methods would be effective in the treatment of chronic HBV infection.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present rejection, the factors considered most relevant are the scope of the claimed invention, the state of the prior art, and the provision of guidance or working examples.

As indicated above, the claims are drawn to methods of treating chronic hepatitis through the administration to a patient chronically infected with HBV a vaccine comprising a T-cell stimulating amount of a chimeric Hepatitis B core (HBc) protein having into its sequence an immunogenic epitope. By requiring that the claimed methods effect the treatment of chronic hepatitis in patients chronically infected with HBV, the claims are requiring that administration of the described HBc molecules results in a therapeutic benefit to the HBV infected individual receiving the treatment.

It is noted that, while the application discusses the use of the described HBc molecules for the treatment of chronic HBV infections (see e.g., pages 36-38), the application nowhere provides any working examples of the HBc molecules according to the present claims. Nor does the application demonstrate or provide any evidence that such particles would be effective in treating a chronic HBV infection.

In contrast to the suggestion in the present application that the described HBc molecules may be used for the treatment of chronic HBc infections, the teachings in the art indicate that more than such an assertion would be required to demonstrate to those in the art that the claimed method would be an effective treatment. For example, several references in the art teach that the only current therapies for chronic HBV infections involve the administration of antiviral drugs such as interferon-alpha. See e.g., Yuen et al., Lancet Infect Dis 1: 232-41, at 233 (Panel 1) (2001); and Sprengers et al., Fundam Clin Pharmacol 19: 17-26, esp. page 17 (2005). Although teachings in the art indicate that potential therapeutic vaccines for HBV infections are under examination, the art also teaches that such therapies have so far show limited efficacy. See e.g., Lebray et al., J Hepatol 39(S1): S151-59, at S156. It is further noted that none of the identified antigens referred to in art represent the HBc antigens of the presently claimed methods. Thus, the art indicates that the state of the art of therapeutic vaccines against chronic HBV infection is such that there is presently insufficient understanding in the art to indicate what antigens or forms of vaccines may eventually be shown useful.

In view of the teachings in the art indicating that the art of chronic HBV therapeutic vaccination is not well understood, that there is no current therapeutic vaccination against chronic HBV, and in view of the lack of any demonstration in the present application as to the efficacy of the claimed methods, the claims are rejected as exceeding the scope for which the application has presented an enabling disclosure. It is therefore suggested that the claims be limited to the induction of an anti-HBV immune response.

16. Claims 18, 28, and 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments wherein domain I of the administered peptide comprises residues 4-75, or 5-75 in addition to an additional N-terminal sequence, does not reasonably provide enablement for embodiments wherein the HBc particles include residues 5-75, but do not include any additional sequences on the N-terminus of the chimeric proteins.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors that may be considered in making a determination as to whether a claimed invention has been enabled by an application were described above. In the present instance, the factors deemed most relevant are the scope of the claims, the presence or absence of working examples and the guidance in the application, and the state of the art.

The rejected claims read on methods of treating chronic hepatitis through the administration of HBc particles, each of which comprises a plurality of HBc molecules. Claim 18, the independent claim, is treated as representative. This claim requires that these HBc particles are capable of self-assembly into particles (i.e., capable of forming into virus-like capsids). The claims require that the HBc particle comprises at least residue 5 of the native HBc sequence, in addition to zero to three cysteines to the N-terminal end of the protein. However, because the presence of the cysteines is optional (note the "zero" limit) the claim also permits embodiments wherein the HBc particle does not comprise a residue in position 4 relative to the native HBc sequence.

With respect to the self-assembly of the HBc particles, the application notes teachings in the art that HBc molecules lacking residue 4 and without an additional N-terminal sequence are not able to form such particles. See e.g., page 11 (end of cross-over paragraph from page 10). Page 49 of the application specifically states that particles do not form if "no additional sequence is present and more that residues 1-3 are deleted from the N-terminus of HBc." I.e., the application states that HBc molecules lacking some residue in position 4 of the HBc sequence are not capable of self-assembly. Further, the application provides no working examples to counter these assertions. Therefore, in view of these teachings, and because the rejected claims permit the absence of residue 4 without requiring the addition of further N-terminal residues, the claims are rejected as exceeding the scope of inventions for which an enabling disclosure has been provided.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1, 18, 28, and 32-35 are rejected under 35 U.S.C. 103(a) as being obvious over Page et al. (WO 01/98333 - of record in the April 2005 IDS). As indicated above, these claims are drawn to methods for the treatment of a chronic Hepatitis B infection through administration of a T-cell stimulating amount of a chimeric HBc polypeptide to the patient. The claims require that the HBc polypeptide is (i) truncated at about residue 140 of the HBc sequence (claim 1) or at any position from residue 140-149 (claim 18, and dependent claims 28, and 32-35), (ii) comprises an insertion of a sequence comprising one or more chemically non-reactive heterologous amino acids (alanine, isoleucine, or leucine- App., page 42) into the immunodominant loop of the HBc polypeptide (residues 75-85), and (iii) includes one to three cysteine residues at an amino acid positions within 30 residues from the C-terminus of the chimeric protein.

The Page reference teaches the making of HBc molecules comprising a deletion of arginine repeat regions, resulting in an HBc polypeptides lacking the sequence of residues 145-182 or of residues 150-182. See e.g., page 6 and claim 4. Thus, the HBc molecules of the reference include the regions corresponding to residues 1-144 or 1-149, with an inserted sequence somewhere within residues 175-185. Independent claim 1 requires that the HBc molecules used in the claimed method includes the sequence from position 85 "through about 140." Because the reference teaches HBc molecules comprising residues 85-144 or 149, the reference teaches molecules comprising at least residues 85-140 as required by claim 1.

Independent claim 18 (and dependent claims 28, and 32-35) requires the presence of a region beginning at residue 86, and ending at any of residues 140-149. This requirement is met for at least the reasons indicated with respect to claim 1. Additionally, because the reference teaches HBc molecules with C-terminal deletions that begin at position 150 (page 6, lines 15-17), the reference teaches truncations wherein the HBc sequence ends at position 149. Thus, the reference specifically teaches HBc variants that meet this limitation of claim 18. Thus, the reference teaches HBc molecules with the modification (i).

The Page reference also teaches that the HBc disclosed HBc molecules comprise a C-terminal cysteine residue. Pages 6-7, and claim 1. The reference therefore teaches an HBc comprising modification (iii).

With respect to modification (ii), it is noted that the reference nowhere specifically refers to the insertion of a non-chemically reactive amino acid residue.

However, the reference does teach embodiments of the polypeptide suitable for use in the treatment of chronic HBV infections comprising an inserted HBV T-cell epitope. Page 15, lines

18-25. The reference teaches that such epitopes may be inserted into the sequence of HBc immunodominant region corresponding to residues 75-85, 78-83, and most preferably between residues 79 and 80 or 80 and 81. Pages 10-11. The reference describes a preferred HBV T-cell containing sequence comprising the T-cell epitope of residues 21-28 of the Pre-S1 HBV sequence. Page 12, lines 23-31, and page 25, Table 2(showing the sequence). It is noted that the indicated T-cell epitope comprises two non-chemically reactive residues- a leucine and an alanine. Although the reference discloses the insertion of this sequence at the C-terminus of the polypeptide, the reference also, as was described above, states that the T-cell epitopes may also be inserted into the immunodominant loop of residues 75-85 of the HBc protein. Thus, modification (ii) of the claimed HBc sequence would have been obvious to those of ordinary skill in the art for the construction of HBc particles to be used in the treatment of chronic HBV infection.

Because the reference teaches that these particles would be useful for the induction of a T-cell response against HBV for the treatment of chronic infection by the virus, it would have been obvious to those of ordinary skill in the art to administer such particles to chronically infected patients, and to maintain the treatment until the T-cell response is induced.

Those of ordinary skill in the art would have been motivated to perform, and had a reasonable expectation of success in the induction of an anti-HBV T-cell response from, the method in view of the teachings of the reference suggesting the administration of such HBC chimers for the treatment of chronic HBV infection. Thus, the teachings of this reference render the claimed invention obvious.

19. Claims 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Page as applied to claims 1, 18, 28, and 32-35 above, and further in view of Johnson et al. (U.S. 6,303,347- of record in the November 2005 IDS). These claims are drawn to methods such as those of claim 1 above, wherein comprises the administration of one or more agonists of either toll-like receptor-4 (TLR-4) or receptor-9 (TLR-9) in addition to the chimeric HBc molecule. The dependent claims further identify the TLR-4 agonist as an aminoalkyl glucosamide phosphate.

The teachings of Page have been described above. As indicated above, the reference renders obvious the claimed methods of administering a T-cell stimulating amount of the described chimeric HBc molecule for the treatment of chronic hepatitis B. However, while the reference suggests the inclusion of adjuvants in the administered composition (page 16, lines 13-14), the reference does not teach or suggest the use of TLR-4 or TLR-9 agonists.

Johnson does teach the use of aminoalkyl glucosamide phosphate (AGP) adjuvants. It is noted that while the reference teaches a slightly different name for the adjuvants (using the term "glucosaminide" instead of "glucosamide" as is used in the present claims), the current application indicates on page 98 (which refers specifically to the Johnson patent) that the same compounds are being referred to. The reference specifically indicates that the AGP adjuvants are useful in augmenting to cell-mediated, as well as antibody, immune responses to an antigen. Column 4, lines 1-6. Thus, it would have been obvious to those in the art to include such adjuvants in the HBc compositions of Page for the induction of anti-HBV T-cell responses for the treatment of chronic HBV infection. Those of ordinary skill in the art would have been motivated to include such a T-cell stimulating adjuvant in the composition so as to increase the efficacy of the HBc molecule in inducing an anti-HBV T-cell response.

Those of ordinary skill in the art would have had a reasonable expectation of success based on the suggestion in the Page reference that an adjuvant be included, and the teachings in Johnson that the AGPs would be effective T-cell stimulating adjuvants. Thus, the combined teachings of these references render the claimed inventions obvious.

20. Claims 1, 18, 28, and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thoma (WO 92/11368) in view of Birkett et al., (6,942,866) and Pumpens et al. (Intervirol 38: 63-74- of record in the April 2005 IDS). As indicated above, the claims read on the treatment of chronic HBV infections through the administration of a T-cell stimulating amount of a chimeric HBV core (HBc) molecule. The claims require three modifications to this administered HBc molecule. The required modifications are that the HBc molecules (i) are truncated at about residue 140 of the HBc sequence (claim 1) or at any position from residue 140-149 (claim 18, and dependent claims 28, and 32-35); (ii) comprise an insertion of a sequence comprising one or more chemically non-reactive heterologous amino acids (alanine, isoleucine, or leucine- App., page 42) into the immunodominant loop of the HBc polypeptide (residues 75-85), and (iii) include one to three cysteine residues at an amino acid positions within 30 residues from the C-terminus of the chimeric protein.

Thoma teaches a method for the treatment of chronic hepatitis B infection through the administration of a chimeric protein comprising a carrier protein fused to a HBV T-cell epitope. See e.g., pages 6 and 7. The reference teaches that the carrier protein is preferable a carrier that forms a particle, and identifies the HBV core protein as such a carrier. Pages 7-8. The reference specifies a particular HBV T-cell epitope from the HBV S1 sequence (SEQ ID NO: 28) which epitope comprises at least one of each of the following chemically non-reactive amino acids: an alanine, and a leucine. Cf: SEQ ID NO: 28 of the reference (page 12) with Blast search results of sequence vs. translated database (showing at least partial amino acid translation of the disclosed nucleotide sequence). Further, the reference teaches that the sequence may be inserted into any of the C-, the N-, or internally to the carrier particle. It is noted that those of ordinary skill in the art would have known that these three positions represent the commonly known positions for insertions into the HBV core protein. See e.g., Pumpens, page 66. Pumpens further specifies that the internal site for epitope insertion is around positions 78-82 (corresponding to the immunodominant loop). From these teachings, it would have been obvious to those of ordinary skill in the art to insert the epitope suggested by the Thoma reference into the region of residues 78-82 of the HBV core protein.

The combined teachings of Thoma and Pumpens therefore suggest a method for the treatment of chronic HBV through the administration of a T-cell epitope comprising non-chemically reactive residues fused into the immunodominant loop of an HBV core protein. I.e., these references suggest a method as claimed wherein the HBc molecule comprises required modification (ii) to the HBc sequence. However, the Thoma reference does not teach or suggest a fusion comprising modifications (i) or (iii) to the HBC molecule.

Birkett teaches a chimeric HBV core protein comprising an inserted malarial epitope into its immunodominant region. See e.g., claim 1. Like Pumpens, Birkett also teaches the insertion of a foreign epitope into the immmunodominant loop of the HBV core protein. See e.g., claim 1 (description of Domain II). Further, both Pumpens and Birkett teach the deletion of certain C-terminal regions of the HBV core protein. Pumpens, page 67; and Birkett, column 7, lines w0-49. However, Birkett teaches that while such deletions confer advantages to the protein with respect to RNA binding, they also result in reduced stability of the resultant truncated proteins. Birkett goes on to teach that addition of C-terminal cysteines to the truncated HBV core sequence results in increased stability of the truncated proteins. Columns 16-17. Thus, the Birkett reference suggests modifications to HBc carrier molecules corresponding to required modifications (i) and (iii) of the present claims. In view of these teachings regarding the reduced RNA-binding, and increased stability of the truncated HBc particles, it would have been obvious to those of ordinary skill in the art to incorporate these modifications to the HBC molecules into the core protein carriers used in the method of Thoma. Those in the art would have been motivated to combine these teachings with those of Thoma to take advantage of the additional benefits of reduced RNA binding and increased stability of the truncated molecules.

Further, because each of the indicated references teaches the disclosed HBc molecules are useful for the induction of an immune response against the inserted epitope, those in the art would have had a reasonable expectation of success in the combination of the teachings of these references.

21. Claims 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thoma in view of Birkett and Pumpens as applied to claims 1, 18, 28, and 32-35 above, and further in view of Johnson. The presently rejected claims have been described above. As indicated above, these

claim read on the method of claim 1, wherein TLR-4 or TLR-9 agonists are administered with the HBc chimer.

The combined teachings of Thoma, Birkett, and Pumpens have also been described above. While Thoma teaches the administration of the HBc molecules for the treatment of chronic HBV infection through the induction of a T-cell response, the reference does not teach the administration of TLR receptor agonists as adjuvants. However, as was described above, the Johnson reference does teach the use of AGPs as adjuvants for T-cell immune responses. It would therefore have been obvious to those of ordinary skill in the art to use such compounds as adjuvants in the T-cell stimulating composition suggested by the combined teachings of Thoma, Birkett, and Pumpens. Those of ordinary skill in the art would have had a reasonable expectation of success in such a use because Johnson teaches that the AGPs are useful adjuvants generally, and would therefore have been expected to be useful adjuvants for the immunogenic particles of Thoma. In view of these teachings, and because the application identifies the agent of Johnson and TLR-4 agonists (pages 98 and 100), the combined teachings of these references render the claimed method obvious.

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In*

re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 1, 18, 28, and 32-35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 27 of copending Application No. 10/312,045. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to an obvious variation of the claim in the copending application. The claim of the copending application is broadly drawn to a method for the vaccination or therapy of a subject by administration of a chimeric HBc protein, wherein the protein has had one or more of the arginine repeats deleted, and wherein a C-terminal cysteine residue is present.

Further, the copending application also provides other teachings similar to those described with respect to the Page reference above. Like Page, the copending application discloses embodiments wherein the polypeptide is used for the treatment of chronic HBV infection through induction of an anti-HBV T-cell response. Page 15, lines 18-25. The application also provides identification of the same HBV T-cell epitope described by the Page reference above. See, pages 12 and 25 of application 10/312,045. In view of these teachings, and for the reasons indicated with respect to the Page reference above, the current claims represent an obvious variation of the method described in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 1, 18, 28, and 32-35 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 24 of copending Application No. 10/326,908. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to an obvious variation of the claim in the copending application. The claim of the copending application is broadly drawn to a method for the immunotherapy of a subject by administration of a chimeric HBc protein.

Although the claim of the copending application does not teach the limitations of the present claims, such limitations are identified as specific embodiments of the HBc molecules that may be used in the specification of that application. See e.g., pages 4-5, and 6-7 (teaching the insertion of heterologous epitopes into the immunodominant loop of the HBV core protein, the deletion of the C-terminal arginine repeats, and the C-terminal cysteines as described above). Further, the reference also teaches that such particles may be used for the treatment of chronic hepatitis. Page 11. Thus, the currently claimed methods represent obvious variations of the method claimed by the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. Claims 48-51 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over either claim 27 of copending Application No. 10/312,045, or over claim 24 of copending Application No. 10/326,908, further in view of the teachings of Johnson et al. (U.S. 6,303,347). The claims have been described above, as have the teachings of each of the copending applications and of the Johnson patent.

As with the Page reference applied above under 35 U.S.C. 103(a), the copending applications also teaches the administration of the chimeric HBc for the treatment of chromic HBV infection, and suggests the inclusion of an adjuvant with the polypeptide ('045 application, page 16 lines 13-14; and the '908 application, page 13 lines 22-24). Also, as with the Page reference, the copending applications do not teach or suggest the use of TLR-4 (including AGPs) or TLR-9 agonists.

However, because Johnson teaches the inclusion of AGPs as adjuvants, and teaches that such compounds are useful in augmenting cellular immune responses against antigens, it would have been obvious to those of ordinary skill in the art to include such adjuvants in compositions used in the methods of these applications. Because the AGPs are identified as TLR-4 agonists by the present application, the inclusion of AGPs in the administrated compositions of these applications meets the addition requirements of claims 48-51. Those in the art would therefore have had a reasonable expectation of success in the use of the AGP adjuvants based on the indication in Johnson that these compounds are useful for augmenting cell-meditated immune responses. Thus, in view of the teachings of Johnson, the indicated claims of the present application represent obvious variations of the claimed methods of the copending applications.

This is a provisional obviousness-type double patenting rejection.

26. The above rejections are, in part, based on the specification of a previously issued patent, rather than the claims. In support of the use of this material, the examiner notes the following excerpt from MPEP section 804 II (B)(1):

> When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. This does not mean that one is precluded from all use of the patent disclosure.
>
> The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Thus, the courts have held that it is permissible to use the specification in determining what is included in, and obvious from, the invention defined by the claim on which the rejection is based. This is true even where elements are drawn from the specification describing the claimed invention which are not elements in the claim itself.

Conclusion

27. No claims are allowed.

28. The following prior art reference is made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Krieg et al., U.S. 6,194,388. This reference teaches the use of unmethylated CpG containing nucleic acids as vaccine adjuvants. Columns 17-18. The reference teaches that such CpG containing oligonucleic acids have T-cell stimulating activity. See e.g., column 15. Thus, the reference would have rendered it obvious to those in the art to administer such as an adjuvant with the HBc molecules of Page. It is also noted that such compounds are identified in the application (page 100) as TLR-9 agonists. Because such agonists are an alternative to the TLR-4 agonists (the AGPs) of Johnson in the current claims, the teachings of Krieg are considered redundant to those of Johnson with respect to the currently pending claims.
>
> Sieling and Modlin, Curr Opin Microbiol 5: 70-75; and Akira et al., Immunol Lett 85: 85-95. These references are considered relevant in that they indicate that the disclosed agonists of the toll-like receptors 4 and 9 in the current application represent the generally accepted target ligands of these receptors. In view of the teachings in the Sieling reference indicating that the TLRs have limited ligand specificity, as the art indicates that the specificity of TLR-4 and TLR-9 are known, and as the teachings in the application identify the known ligands as the "agonists" used in the claims, there appears to be sufficient support for the claim language reading on agonists of these receptors.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner